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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/720,904	11/24/2003	George Sgouros	D6348CIP	5297

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EXAMINER	
PERREIRA, MELISSA JEAN	
ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/720,904	SGOUROS ET AL.	
	Examiner	Art Unit	
	MELISSA PERREIRA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-59* is/are pending in the application.

4a) Of the above claim(s) *1-19 and 34-59* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-59 are pending in the application. Claims 1-19 and 34-59 are withdrawn from consideration. Any objections and/or rejections from previous office actions that have not been reiterated in this office action are obviated.

Response to Arguments

1. Applicant's arguments filed 2/29/08 have been fully considered but they are not persuasive.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Larsen et al. (US 6,592,843) in view of Scheinberg et al. (6,683,162B2) and Wartchow et al. (US2003/0082103A1).

4. The Applicant asserts that Larsen *et al.* does not teach or disclose radiolabeled small liposomes contained within a large liposome of sufficient size to retain a majority of radioactive decay intermediates, which together produce a multivesicular liposome. Further, Applicant asserts that Larsen *et al.* does not teach or disclose passive entrapment of chelated Ac-225 into small liposomes but rather specify an ionophore is required to actively transport the radionuclide across the lipid

bilayer. Finally, Larsen *et al.* does not teach or disclose antibodies such as HERCEPTIN ® to allow targeting specificity of radiolabeled multivesicular liposomes to tumor cells.

5. The reference of Larsen *et al.* was not used to teach or disclose radiolabeled small liposomes contained within a large liposome of sufficient size to retain a majority of radioactive decay intermediates, which together produce a multivesicular liposome. The reference of Larsen *et al.* was used to teach of the encapsulation of radionuclide-chelator complexes that emit alpha particles, such as ^{212}Pb, ^{225}Ac into a liposome to generate a radionuclide-liposome conjugator system with PEG affinic groups. The reference of Wartchow et al. was used to teach of liposomes (bilayer or multilamellar vesicles) that may have the therapeutic agent/radionuclide-chelator complexes encapsulated (p9, [0075]; p10, [0078-0079]) within or trapped in the core of the liposome. For example, Wartchow et al. discloses that the therapeutic entity (i.e. radionuclide-chelator complex) may be entrapped or encapsulated within (p8, [0056]). The encapsulation of a radionuclide-conjugator complex within the multilamellar vesicles of Wartchow et al. provides for the limitation of a radiolabeled small liposome contained within a large liposome as the multilamellar vesicles have an onion like form (p10, [0078]). The references of Larsen *et al.* and Wartchow et al. are drawn to radionuclide-chelator liposomal conjugator systems and therefore it would be obvious to one skilled in the art that the radionuclide-conjugator complex containing liposomes of Larsen et al. may be multilamellar and thus contain a radiolabeled small liposome within

a large liposome and one skilled in the art would have a reasonable expectation of success for preparing such a multilamellar liposome.

6. The instant claims do not exclude an ionophore to actively transport the radionuclide across the lipid bilayer.

7. The reference of Larsen *et al.* was not used to teach or disclose antibodies such as HERCEPTIN ® to allow targeting specificity of radiolabeled multivesicular liposomes to tumor cells. The references of Scheinberg et al. and Wartchow et al. both teach that radionuclide-chelator complexes may be attached to targeting entities (i.e. antibodies such as HERCEPTIN ®). Wartchow et al. further teaches that antibody-radionuclide-chelator complexes may be included within a multilamellar liposome. Therefore in combination, it would be obvious to one skilled in the art that an attached antibodies such as HERCEPTIN ®) to a radionuclide-chelator complex contained within a multilamellar liposomal construct for site-specific targeting.

8. Applicant asserts that Scheinberg et al. does not disclose use of Ac-225 entrapment in liposomes nor disclose retention of radioactive decay intermediates in multivesicular liposomes.

9. The reference of Scheinberg et al. was not used to teach or disclose use of Ac-225 entrapment in liposomes nor disclose retention of radioactive decay intermediates in multivesicular liposomes.

10. . The reference of Larsen *et al.* was used to teach of the encapsulation of radionuclide-chelator complexes that emit alpha particles, such as ^{212}Pb, ^{225}Ac into a liposome to generate a radionuclide-liposome conjugator system with PEG affinic groups. The reference of Scheinberg et al. was used to teach that radionuclide-chelator complexes may be attached to targeting entities (i.e. antibodies such as HERCEPTIN ®). In combination, it would be obvious that the radionuclide-chelator complexes of Larsen et al. (encapsulated within a liposome) may be attached to an antibody (such as HERCEPTIN ®) for site-specific targeting.

11. The reference of Wartchow et al. was used to teach of the encapsulation of a HERCEPTIN ®-radionuclide-conjugator complex within the multilamellar vesicles. The references of Larsen *et al.* and Wartchow et al. are drawn to radionuclide-chelator liposomal conjugator systems and therefore it would be obvious to one skilled in the art that the liposomes of the combined references of Larsen et al. and Scheinberg et al. may be multilamellar and one skilled in the art would have a reasonable expectation of success for preparing such a multilamellar liposome.

12. Applicant asserts that Wartchow et al. does not disclose use of 1000nm liposomes but rather disclose production of very large multilamellar vesicles of 1000-10,000 nm as a step in the process of making the correctly sized unilamellar liposomal vesicles of 50-100nm for maximum in vivo circulation time ([0078]). Further, Wartchow et al. disclose large multilamellar vesicles are rapidly removed from circulation by the reticuloendothelial system (liver and spleen) thus

the Wartchow et al. invention typically utilize unilamellar vesicles having an average diameter of less than 200nm, preferably less than IOOnm, and even more preferably 60-80 nm so that they will remain in circulation for hours ([0079]).

13. Wartchow et al. discloses that both multilamellar liposomes and unilamellar liposomes are generated. The unilamellar liposomes may be generated by sonication of the multilamellar liposomes (of size 1000-10,000 nm) but are not necessarily generated. Wartchow et al. discloses that both multilamellar liposomes and unilamellar liposomes are valuable vehicles for drug delivery ([0079]) and therefore it would be obvious to utilize the multilamellar liposomes described and not necessarily convert them to unilamellar liposomes.

14. Applicant asserts that taken together, Larsen *et* al., Scheinberg *et* al., and Wartchow *et* al., provide no motivation to use large multivesicular liposomes to contain the radionuclide parent and daughter particles.

15. The large multilamellar liposomes (containing a PEG stabilizing entity) of Wartchow *et* al., are taken up by the reticuloendothelial system whereas the smaller liposomes (containing a PEG stabilizing entity) of Larsen *et* al. reduced the recognition and clearance affected by the macrophases of the reticuloendothelial system. Therefore it would be obvious to utilize a larger multilamellar liposomes (containing a PEG stabilizing entity) to specifically direct the liposome to the reticuloendothelial system. The instant claims are drawn to directing the liposomes to the

reticuloendothelial organs and therefore the large multilamellar liposomes of the combined disclosures encompass the liposomes of the instant claims.

Conclusion

No claims are allowed at this time.

16. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA PERREIRA whose telephone number is (571)272-1354. The examiner can normally be reached on 9am-5pm M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Melissa Perreira/
Examiner, Art Unit 1618